SUPPLEMENTARY DATA

Supplementary Material

A randomized trial evaluating the efficacy and safety of fast-acting insulin aspart compared with insulin aspart, both in combination with insulin degludec with or without metformin, in adults with type 2 diabetes (onset 9)

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Supplementary Table 1. Basal insulin titration algorithm

Mean pre-breakfast SMBG values		Dose adjustment
mmol/L	mg/dL	U
<3.1	<56	–4
3.1–3.9	56–70	–2
4.0–5.0	**71–90**	**No adjustment**
5.1–7.0	91–126	+2
7.1–8.0	127–144	+4
8.1–9.0	145–162	+6
>9.0	>162	+8

Adjustments were made once weekly by the investigator during the run-in period.
SMBG values are plasma-equivalent glucose values.
SMBG, self-measured blood glucose.

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Supplementary Table 2. Bolus insulin titration algorithm

Pre-prandial or bedtime SMBG values		Dose adjustment	Rules for dose adjustment
mmol/L	mg/dL	U	
<4.0	<71	−1	≥1 SMBG below target
4.0–6.0	71–108	0	0−1 SMBG above target No SMBGs below target
>6.0	>108	+1	≥2 SMBGs above target No SMBGs below target

Adjustments were made twice weekly, once by the investigator and once by the participant. SMBG values are plasma-equivalent glucose values.
SMBG, self-measured blood glucose.

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Supplementary Table 3. Trial endpoints (pre-specified)

Primary endpoint (16 weeks after randomization)	• Change from baseline in HbA_{1c}
Confirmatory secondary endpoints (16 weeks after randomization)	• Change from baseline in 1-h PPG increment (meal test) • Change from baseline in 1,5-anhydroglucitol
Supportive secondary efficacy endpoints (16 weeks after randomization)	• Change from baseline in FPG • Percentage of participants reaching HbA_{1c} targets: – HbA_{1c} <7.0% (53 mmol/mol) – HbA_{1c} <7.0% (53 mmol/mol) without severe hypoglycemia • Change from baseline in 30-min, 1-h, 2-h, 3-h and 4-h PPG and in 30-min, 2-h, 3-h and 4-h PPG increment (meal test) • Change from baseline in 7-9-7-point SMBG profile assessed by: – Mean of the 7-9-7-point profile – PPG and PPG increment (mean, breakfast, lunch, and main evening meal) • Percentage of participants reaching PPG targets: – 1-h PPG ≤7.8 mmol/L (140 mg/dL) – 1-h PPG ≤7.8 mmol/L (140 mg/dL) without severe hypoglycemia

	• Insulin dose
Supportive secondary safety endpoints (16 weeks after randomization)	• Number of treatment-emergent adverse events • Number of treatment-emergent injection-site reactions • Number of treatment-emergent hypoglycemic episodes: – Overall – Daytime – Nocturnal (00:01–05:59 inclusive) – Meal-related from start of meal until 1, 2, and 4 h after start of meal • Change from baseline in clinical evaluation: – Physical examination ▪ Head, ears, eyes, nose, throat, neck, respiratory system, cardiovascular system, gastrointestinal system including mouth, musculoskeletal system, central and peripheral nervous system, and skin. – Vital signs ▪ Diastolic blood pressure, systolic blood pressure, and pulse – Electrocardiogram – Fundoscopy/fundus photography • Change from baseline in body weight and BMI

	• Change from baseline in central laboratory assessments: – Hematology (hemoglobin, hematocrit, erythrocytes, thrombocytes, and leucocytes) – Biochemistry (alanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, creatinine, potassium, sodium, total bilirubin, total protein)

Adverse events were defined as treatment-emergent if the onset date occurred on or after the first day of exposure to randomized treatment, and no later than seven days after the last day of exposure to randomized treatment. Hypoglycemic episodes were defined as treatment ‐ emergent if the onset of the episode occurred on or after the first day of exposure to randomized treatment and no later than one day after the last day of exposure to randomized treatment.
FPG, fasting plasma glucose; PPG, postprandial glucose; SMBG, self-measured blood glucose.

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Supplementary Table 4. Confirmatory statistical analysis

Endpoint [comparison]		**Estimate [95% CI]**	**Conclusion**
Step 1	**Change from baseline in HbA_{1c} 16 weeks after randomization (%)** [faster aspart–insulin aspart]	–0.04 [–0.11; 0.03]	*Non-inferiority confirmed with one-sided P-value <0.001*
Step 2	**Change from baseline in 1-h PPG increment 16 weeks after randomization (meal test) (mmol/L)** [faster aspart–insulin aspart]	–0.40 [–0.66; –0.14]	*Superiority confirmed with one-sided P-value 0.001*
Step 3	**Change from baseline in HbA_{1c} 16 weeks after randomization (%)** [faster aspart–insulin aspart]	–0.04 [–0.11; 0.03]	*Superiority not confirmed with one-sided P-value 0.155*
Step 4	**Change from baseline in 1,5-anhydroglucitol 16 weeks after randomization (µg/mL)** [faster aspart–insulin aspart]	0.50 [0.11; 0.89]	*Testing procedure stopped*

P-values are from the one-sided test for non-inferiority and superiority, respectively, evaluated at the 2.5% level.
Faster aspart, fast-acting insulin aspart; PPG, postprandial glucose.

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Supplementary Table 5. Results summary of supportive endpoints

	Faster aspart, % of participants	**Insulin aspart, % of participants**	**Estimated OR [95% CI] (Faster aspart/insulin aspart)**
HbA_{1c} responders 16 weeks after randomization			
HbA_{1c} <7.0% (53 mmol/mol)	49.6	51.7	1.12 [0.83; 1.49]
HbA_{1c} <7.0% (53 mmol/mol) without severe hypoglycemia	48.5	51.0	1.08 [0.81; 1.44]
PPG responders 16 weeks after randomization			
PPG ≤7.8 mmol/L (140 mg/dL)	34.1	35.2	0.99 [0.75; 1.31]
PPG ≤7.8 mmol/L (140 mg/dL) without severe hypoglycemia	33.3	34.9	0.97 [0.73; 1.29]
	Faster aspart, mean	**Insulin aspart, mean**	**ETD [95% CI] (Faster aspart–insulin aspart)**
Change from baseline 16 weeks after randomization			
30-min PPG increment (meal test),			
mmol/L	–0.13	–0.05	–0.07 [–0.26; 0.12]
mg/dL	–2.29	–0.84	–1.29 [–4.71; 2.13]
2-h PPG increment (meal test),			
mmol/L	–0.37	0.001	–0.30 [–0.62; 0.02]
mg/dL	–6.67	0.01	–5.42 [–11.26; 0.42]
3-h PPG increment (meal test),			
mmol/L	–0.15	0.28	–0.29 [–0.64; 0.06]
mg/dL	–2.73	5.07	–5.20 [–11.54; 1.13]
4-h PPG increment (meal test),			
mmol/L	0.04	0.15	–0.05 [–0.39; 0.30]
mg/dL	0.72	2.69	–0.87 [–7.11; 5.37]

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30-min PPG (meal test),			
mmol/L	0.31	0.55	–0.16 [–0.46; 0.14]
mg/dL	5.62	9.87	–2.58 [–8.28; 2.58]
1-h PPG (meal test),			
mmol/L	0.03	0.68	–0.47 [–0.81; –0.13]*
mg/dL	0.62	12.27	–8.47 [–14.68; –2.27]*
2-h PPG (meal test),			
mmol/L	0.08	0.61	–0.39 [–0.78; –0.002]†
mg/dL	1.51	11.02	–7.02 [–14.00; –0.04]†
3-h PPG (meal test),			
mmol/L	0.30	0.89	–0.38 [–0.79; 0.02]
mg/dL	5.47	16.04	–6.93 [–14.17; 0.31]
4-h PPG (meal test),			
mmol/L	0.51	0.75	–0.14 [–0.52; 0.24]
mg/dL	9.12	13.57	–2.46 [–9.30; 4.39]
Mean 7-9-7-point SMBG profile,			
mmol/L	–0.56	–0.50	0.01 [–0.17; 0.19]
mg/dL	–10.06	–8.95	0.18 [–2.99; 3.34]
1-h PPG (SMBG, breakfast),			
mmol/L	–0.38	–0.28	–0.07 [–0.35; 0.20]
mg/dL	–6.85	–5.11	–1.31 [–6.28; 3.65]
1-h PPG (SMBG, lunch),			
mmol/L	–0.78	–0.58	–0.17 [–0.43; 0.09]
mg/dL	–14.07	–10.40	–3.02 [–7.69; 1.64]
1-h PPG (SMBG, main evening meal),			
mmol/L	–1.04	–0.71	–0.11 [–0.37; 0.14]
mg/dL	–18.82	–12.85	–2.04 [–6.66; 2.59]
1-h PPG (SMBG, all meals),			

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mmol/L	–0.75	–0.52	–0.14 [–0.35; 0.07]
mg/dL	–13.49	–9.28	–2.58 [–6.36; 1.20]
1-h PPG increment (SMBG, breakfast),			
mmol/L	–0.56	–0.42	–0.14 [–0.38; 0.10]
mg/dL	–10.14	–7.66	–2.47 [–6.80; 1.87]
1-h PPG increment (SMBG, lunch),			
mmol/L	–0.38	–0.23	–0.32 [–0.57; –0.07]‡
mg/dL	–6.85	–4.16	–5.73 [–10.19; –1.27]‡
1-h PPG increment (SMBG, main evening meal),			
mmol/L	–0.44	–0.10	–0.27 [–0.51; –0.03]§
mg/dL	–7.90	–1.79	–4.80 [–9.14; –0.47]§
1-h PPG increment (SMBG, all meals),			
mmol/L	–0.48	–0.23	–0.25 [–0.42; –0.09]¶
mg/dL	–8.66	–4.14	–4.58 [–7.59; –1.57]¶
1,5-anhydroglucitol, µg/mL	1.38	0.89	0.50 [0.11; 0.89]‡
FPG,			
mmol/L	0.56	0.68	–0.03 [–0.28; 0.22]
mg/dL	10.06	12.31	–0.47 [–4.99; 4.04]

*$P = 0.007$, †$P = 0.049$, ‡$P = 0.012$, §$P = 0.03$, ¶$P = 0.003$.
All available information regardless of treatment discontinuation or use of ancillary treatment was used. SMBG measurements are plasma-equivalent glucose values.
Faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; OR, odds ratio; PPG, postprandial glucose; SMBG, self-measured blood glucose

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Supplementary Table 6. Daily bolus, basal and total insulin dose (actual) at week 1 and week 16

Visit	Treatment	Insulin dose					
		N	Mean	SD	Median	Min	Max
Bolus dose (all meals), U							
Week 1	Faster aspart	530	40.64	28.45	33.83	3.0	227.3
	Insulin aspart	523	40.05	27.45	33.00	0.0	243.3
Week 16	Faster aspart	544	54.72	35.82	44.00	3.3	240.0
	Insulin aspart	542	53.38	35.35	45.00	3.0	381.0
Basal dose, U							
Week 1	Faster aspart	531	64.98	34.32	58.67	5.0	230.0
	Insulin aspart	530	64.92	35.61	60.17	7.7	348.0
Week 16	Faster aspart	544	63.76	35.21	58.00	0.0	230.0
	Insulin aspart	542	62.25	36.03	58.00	4.7	348.0
Total insulin dose, U							
Week 1	Faster aspart	528	105.79	54.50	96.17	16.3	457.3
	Insulin aspart	522	105.13	56.12	96.33	13.7	591.3
Week 16	Faster aspart	544	118.52	64.20	104.00	15.7	470.0
	Insulin aspart	542	115.63	65.09	105.33	20.0	729.0
Bolus dose (all meals), U/kg							
Week 1	Faster aspart	530	0.43	0.26	0.37	0.0	2.0
	Insulin aspart	523	0.42	0.26	0.37	0.0	2.4
Week 16	Faster aspart	544	0.57	0.33	0.48	0.0	2.0
	Insulin aspart	542	0.55	0.34	0.49	0.1	3.7
Basal dose, U/kg							
Week 1	Faster aspart	531	0.68	0.32	0.64	0.1	1.9
	Insulin aspart	530	0.67	0.33	0.65	0.1	3.4
Week 16	Faster aspart	544	0.66	0.32	0.61	0.0	1.9
	Insulin aspart	542	0.64	0.32	0.60	0.1	3.4
Total insulin dose, U/kg							
Week 1	Faster aspart	528	1.11	0.48	1.01	0.3	2.9
	Insulin aspart	522	1.10	0.50	1.02	0.2	5.8
Week 16	Faster aspart	544	1.23	0.57	1.10	0.2	3.3
	Insulin aspart	542	1.19	0.59	1.10	0.3	7.0

Based on data collected up to 7 days after the last dose of randomized treatment or the day before initiation of ancillary treatment.

Faster aspart, fast-acting insulin aspart; N, number of participants; SD, standard deviation.

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Supplementary Table 7. Treatment-emergent adverse events

	Faster aspart				Insulin aspart			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
All AEs	276	50.7	667	4.015	272	50.0	643	3.865
Serious	38	7.0	56	0.337	40	7.4	58	0.349
Severe	21	3.9	32	0.193	20	3.7	31	0.186
Injection-site reactions	7	1.3	7	0.042	4	0.7	8	0.048
Allergic reactions	9	1.7	9	0.054	7	1.3	9	0.054

Adverse events were defined as treatment‐emergent if the onset of the event occurred on or after the first day of exposure to randomized treatment and no later than 7 days after the last day of exposure to randomized treatment. Serious AE was defined as an experience that at any dose resulted in any of the following: death; a life-threatening experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability or incapacity; a congenital anomaly or birth defect; or an event that may have jeopardized the participant and may have required medical or surgical intervention to prevent one of the outcomes listed above. A severe AE was defined as an event that caused considerable interference with daily activities.

%, percentage of participants; AE, adverse event; E, number of events; faster aspart, fast-acting insulin aspart; N, number of participants; R, event rate per patient-year of exposure.

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Supplementary Table 8. Treatment-emergent medication errors

	Faster aspart				Insulin aspart			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
All events	36	6.6	40	0.241	14	2.6	16	0.096
Wrong product administered	26	4.8	29	0.175	12	2.2	13	0.078
Incorrect dose administered	3	0.6	3	0.018	1	0.2	1	0.006
Accidental overdose	3	0.6	3	0.018	0	–	–	–
Medication error	2	0.4	2	0.012	1	0.2	1	0.006
Overdose	1	0.2	2	0.012	0	–	–	–
Wrong dose	1	0.2	1	0.006	0	–	–	–
Device malfunction	0	–	–	–	1	0.2	1	0.006

A medication error was defined as: the administration of wrong drug; the wrong route of administration; an overdose with the intention to cause harm, misuse or abuse of trial product; or accidental administration of a lower or higher dose than intended to an extent where clinical consequences were likely to happen as judged by the investigator. A medication error was defined as treatment‐emergent if the onset of the event occurred on or after the first day of exposure to randomized treatment and no later than 7 days after the last day of exposure to randomized treatment.

%, percentage of participants; E, number of events; faster aspart, fast-acting insulin aspart; N, number of participants; R, event rate per patient-year of exposure.

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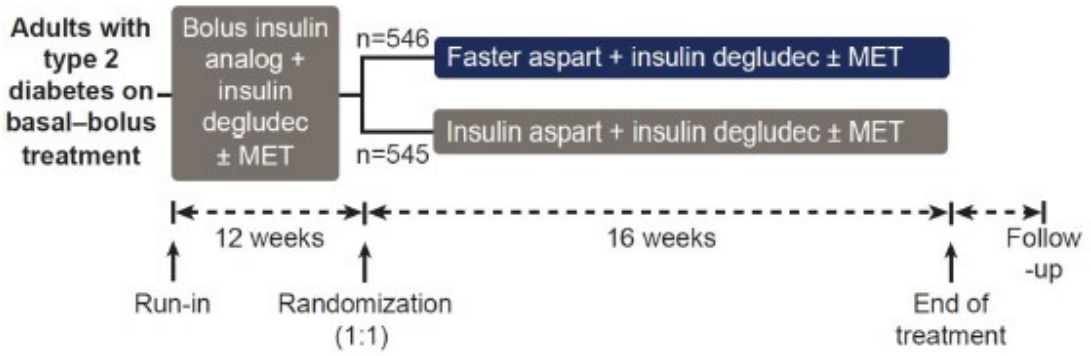
Supplementary Figure 1. Trial design



ClinicalTrials.gov: NCT03268005. Baseline is at randomization. Follow-up occurred at 7 and 30 days after end of treatment.

Faster aspart; fast-acting insulin aspart; MET, metformin.

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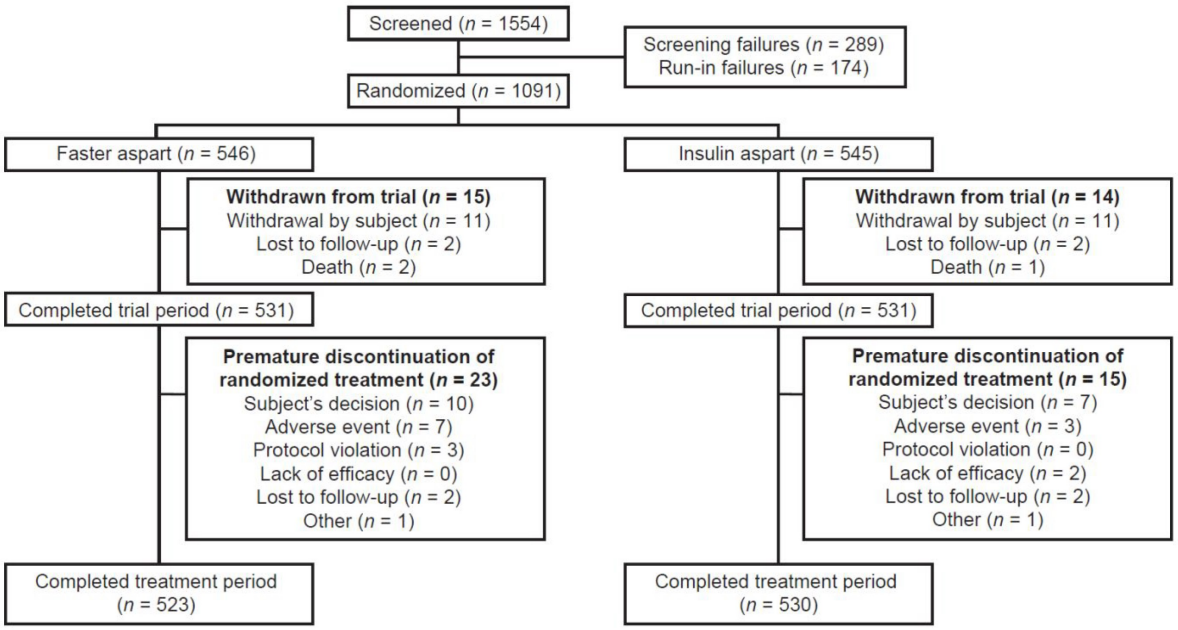
Supplementary Figure 2. Participant disposition



Treatment period: the period from week 0 to week 16 without premature discontinuation of randomized treatment.
Trial period: the period from week 0 to week 16.
Faster aspart, fast-acting insulin aspart; n, number of participants.

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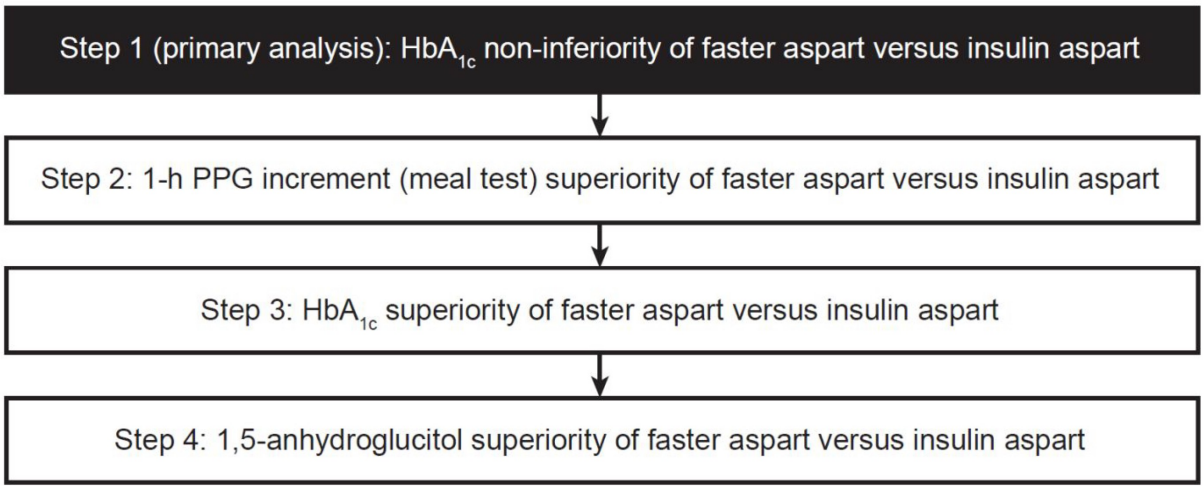
Supplementary Figure 3. Stepwise hierarchical testing procedure for confirmatory hypotheses



All available information regardless of treatment discontinuation or use of ancillary treatment was used. Once non-inferiority (0.4% margin) of faster aspart versus IAsp was confirmed in terms of change from baseline in HbA_{1c} 16 weeks after randomization (step 1), the confirmatory statistical analyses could proceed to the next step. Superiority of faster aspart versus IAsp in terms of 1-h PPG increment assessed using a meal test (step 2) was also confirmed. The hierarchical (fixed-sequence) testing was based on a priority ordering of the null-hypotheses – testing using the two-sided 95% CI approach until an insignificant result appeared. As superiority of faster aspart in terms of the change from baseline in HbA_{1c} (step 3) could not be confirmed, the hierarchical statistical testing procedure was stopped.

Faster aspart, fast-acting insulin aspart; IAsp, insulin aspart; PPG, postprandial glucose.

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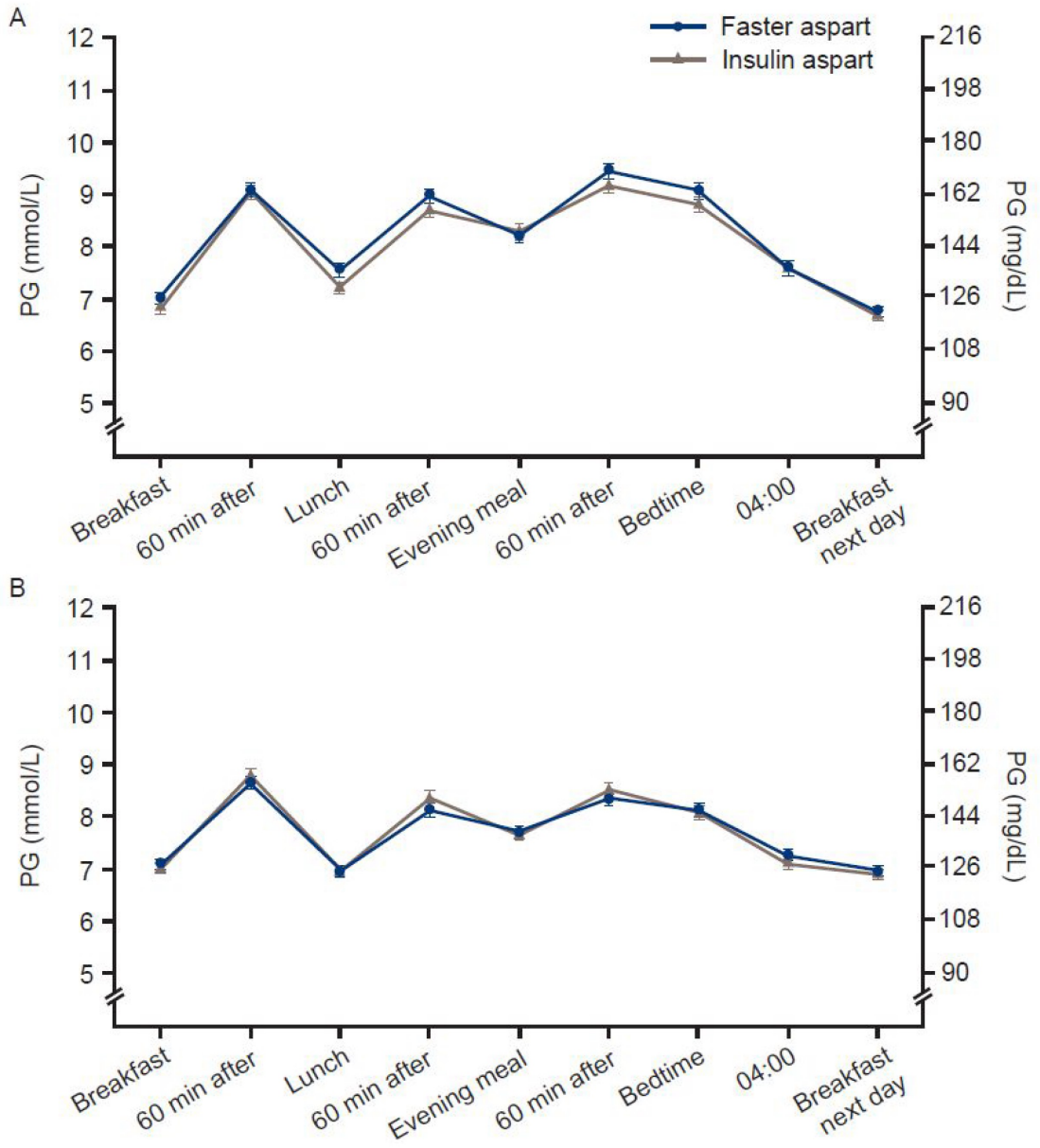
Supplementary Figure 4. Nine-point SMBG profiles at baseline (A) and week 16 (B) with faster aspart and insulin aspart



Error bars: ± standard error (mean).
All available information regardless of treatment discontinuation or use of ancillary treatment was used. SMBG measurements are plasma-equivalent glucose values.
Faster aspart, fast-acting insulin aspart; PG, plasma glucose; SMBG, self-measured blood glucose.

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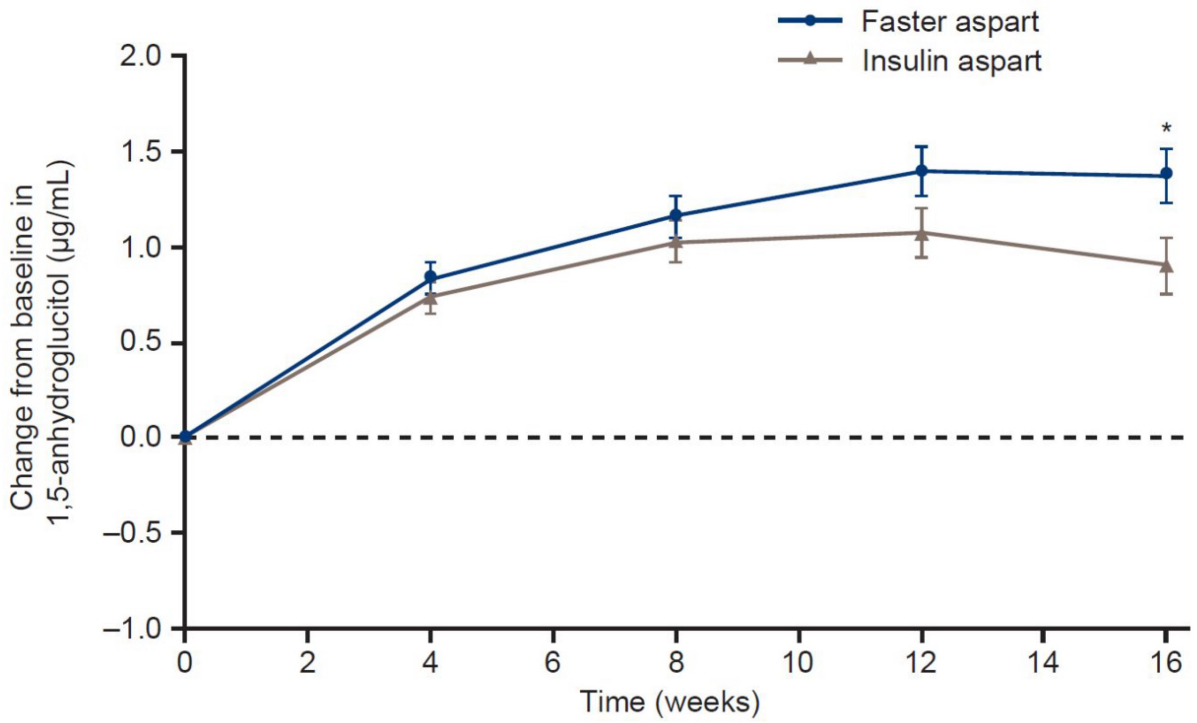
Supplementary Figure 5. Change from baseline in 1,5-anhydroglucitol over time



Error bars: ± standard error (mean).
All available information regardless of treatment discontinuation or use of ancillary treatment was used.
*Estimated treatment difference [95% CI] was 0.50 µg/mL [0.11;0.89]; *P* = 0.012.
Faster aspart, fast-acting insulin aspart

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Supplementary Appendix

Full inclusion criteria

1. Informed consent obtained before any trial-related activities. Trial-related activities were any procedures carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age ≥18 years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus ≥10 years prior to screening.
4. Treated with a basal-bolus insulin regimen ≥1 year prior to the day of screening. A basal-bolus insulin regimen was defined as basal insulin once or twice daily and bolus insulin analog taken with meals at least 3 times daily. Treatment with premixed insulin or soluble insulin combination was not considered a basal-bolus regimen.
5. Treated with or without oral antidiabetic drugs including extended release formulations.
6. HbA_{1c} 7.0–10.0% (both inclusive) as assessed by central laboratory at screening.
7. Able and willing to adhere to the protocol including performance of SMBG profiles and meal test.
8. Able and willing to consume three main meals (breakfast, lunch and dinner) daily throughout the trial.

Full exclusion criteria

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who was pregnant, breastfeeding or intended to become pregnant or was of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

For Bulgaria, Czech Republic, Germany, Greece, Italy, Poland, Romania and Spain: The following contraceptive measures were considered adequate:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, transdermal or intravaginal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- sexual abstinence
- vasectomized partner
- double barrier method (a combination of male condom with either cap, diaphragm or sponge with spermicide)

4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening. Clinical trials do not include non-interventional studies.
5. Any disorder, except for conditions associated with type 2 diabetes, which in the investigator's opinion might jeopardize participant's safety or compliance with the protocol.
6. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischemic attack within the past 180 days prior to the day of screening.
7. Participants presently classified as being in New York Heart Association Class IV.
8. Planned coronary, carotid or peripheral artery revascularization known on the day of screening.
9. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening.
10. Treatment with injectable GLP-1 receptor agonists in a period of 90 days prior to screening.
11. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or

corticosteroids).

12. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or pharmacologically dilated fundoscopy performed within the past 90 days prior to start of run-in period.

13. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma *in situ* was allowed.

14. For subjects treated with metformin: any contraindications or restrictions to use of metformin (according to local labelling) at investigator's discretion.

Randomization criterion

1. HbA_{1c} ≤9.0% (75 mmol/mol) measured by the central laboratory at week −1.

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Statistical analyses

Sample size calculations

The sample size was determined to ensure a sufficient power for step 1 and step 2 in the hierarchal testing procedure. The following assumptions were used for the sample size calculations:

	Statistical test	Significance level	Analysis population	Non-inferiority margin	SD	Mean difference	Randomization scheme
Step 1	2-group t-test	One-sided 2.5%	FAS	0.4% (absolute)	0.8%	–0.1%	1:1
Step 2	2-group t-test	Two-sided 5.0%	FAS	NA	3.5 mmol/L	0.6 mmol/L	1:1
Step 3	2-group t-test	Two-sided 5.0%	FAS	NA	0.8%	–0.1%	1:1
Step 4	2-group t-test	Two-sided 5.0%	FAS	NA	3.5 μg/mL	0.2 μg/mL	1:1

FAS, full analysis set; NA, not applicable; SD, standard deviation.

As trials in this population where data from treatment withdrawn subjects was retrieved was limited, a conservative estimate of the standard deviation (SD) in change from baseline in HbA_{1c} of 0.8% was chosen. The power for superiority in step 3 was calculated using the same assumptions as for step 1, but without the non-inferiority margin.

For determination of power in step 2 and 4, SDs of 3.5 mmol/L (63 mg/dL) and 3.5 μg/mL, respectively, were considered reasonable based on previous faster aspart trials.

Based on t-statistics under the above assumptions, 1072 participants in the full analysis set (536 participants per arm) gave marginal power of >99.9% to show non-inferiority in step 1, and marginal power of 80.1% to show superiority in step 2. Assuming a screening failure rate of 30% and run-in failure rate of 15%, 1803 subjects should be screened for inclusion in the trial.

Confirmatory analyses

Hierarchical testing procedure:

- Step 1 (primary analysis): change from baseline in HbA_{1c} 16 weeks after randomization non-inferiority of faster aspart versus insulin aspart was analyzed using an analysis of variance model after multiple imputations assuming treatment according to randomization. The model included treatment, region and metformin use at baseline (yes/no) factors, and baseline HbA_{1c} as a covariate. Multiple imputation was used to sequentially impute missing values of change from baseline in HbA_{1c} to subsequent planned post-baseline visits for each treatment group separately with region and metformin use at baseline (yes/no) as factors, and baseline HbA_{1c} and earlier changes from baseline in HbA_{1c} as covariates. Each imputed dataset was analyzed separately and estimates were combined using Rubin's rules. The pre-defined non-inferiority margin for HbA_{1c} was 0.4%.
- Step 2: change from baseline in 1-h PPG increment 16 weeks after randomization (meal test) superiority of faster aspart compared with insulin aspart was analyzed using an analysis of variance model after multiple imputation assuming participants on faster aspart switch to insulin aspart. The model included treatment, region and metformin use at baseline (Yes/No) as factors and baseline 1-h PPG increment as covariate. Multiple imputation is used to impute missing values of change from baseline in 1-h PPG increment to week 16 based on participants in the insulin aspart arm who completed the trial period. Each imputed dataset was analyzed separately and estimates were combined using Rubin's rules.

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- Step 3: change from baseline in HbA_{1c} 16 weeks after randomization superiority of faster aspart compared to insulin aspart was analyzed using the same model as in step 1 but superiority was confirmed if the upper boundary of the two-sided 95% CI of the mean treatment difference was <0%.
- Step 4: change from baseline in 1,5-anhydroglucitol 16 weeks after randomization superiority of faster aspart versus insulin aspart was analyzed using a model similar to step 1.

The trial also addressed the treatment effect if all participants had taken the treatment as directed and did not initiate ancillary treatment during the 16 weeks (data not shown). The results were similar to the results from the primary analysis due to the high completion rate of the treatment period; therefore, this manuscript does not present the results for this different target of estimation.

Supportive secondary efficacy endpoints

Participants achieving HbA_{1c} <7.0% (53 mmol/mol) or HbA_{1c} <7.0% (53 mmol/mol) without severe hypoglycemic episodes, and 1-h PPG ≤7.8 mmol/L (140 md/dL) or 1-h PPG ≤7.8 mmol/L (140 md/dL) without severe hypoglycemic episodes were analyzed using a logistic regression model with treatment, region and metformin use (yes/no) as factors, and corresponding baseline as a covariate. Participants without a measurement at week 16 were considered not to have achieved target. Change from baseline 16 weeks after randomization in FPG and endpoints derived from the 7-9-7-point SMBG profile were analyzed separately using a model similar to step 1, except with the corresponding baseline as covariate. Change from baseline in PPG and PPG increment (meal test) 16 weeks after randomization was analyzed separately using a model similar to step 2.

Supportive secondary safety endpoints

Treatment-emergent severe or BG-confirmed hypoglycemic episodes were analyzed based on the full analysis set using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycemic episode was considered treatment-emergent as offset. The model included treatment, region and metformin use at baseline (yes/no) as factors. Treatment-emergent adverse events and injection site reactions were summarized descriptively. Physical examination, electrocardiogram, vital signs, fundus photography/fundoscopy and clinical laboratory assessments (hematology and biochemistry) were also summarized descriptively. Change from baseline in body weight was analyzed based on the safety analysis set using a model similar to step 1 in the hierarchical testing procedure, with the corresponding baseline value as covariate.

SUPPLEMENTARY DATA

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